Net Case

Sneddon syndrome associated with Protein S deficiency

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ABSTRACT

Sneddon syndrome (SS) is rare, arterio-occlusive disorder characterized by generalized livedo racemosa of the skin and various central nervous symptoms due to occlusion of medium-sized arteries of unknown. Seizure, cognitive impairment, hypertension, and history of repetitive miscarriages are the other symptoms seen in this disease. Livedo racemosa involves persisting irreversible skin lesions red or blue in color with irregular margins. Usually, SS occurs in women of childbearing age. Protein S deficiency is an inherited or acquired disorder associated with an increased risk of thrombosis. We present a 33-year-old woman with SS with diffuse livedo racemosa, recurrent cerebrovascular diseases, migraine-type headache, sinus vein thrombosis, and protein S deficiency. Protein S deficiency and with Sneddon syndrome rarely encountered in the literature.

Key words: Antiphospholipid antibodies, ischemic cerebrovascular disease, livedo racemosa, protein S deficiency, Sneddon syndrome

INTRODUCTION

Sneddon syndrome (SS) is a disease characterized by two main features, diffuse livedo racemosa and ischemic cerebrovascular disease.[1] In 1907 Ehrmann distinguished two different patterns of livedo: The pathological livedo racemosa and the physiological livedo reticularis. The spectrum of differential diagnosis in patients with livedo reticularis (especially cutis marmorata and amantadine-induced livedo reticularis) and livedo racemosa (especially Sneddon's syndrome, Divry-van Bogaert syndrome, systemic lupus erythematosus, antiphospholipid antibody syndrome, polyarteritis nodosa, cholesterol embolization syndrome, livedoid vasculopathy and haematological diseases) is provided.[2] Sneddon Syndrome is rare, arterioocclusive disorder characterized by generalized livedo racemosa of the skin and various central nervous symptoms due to occlusion of medium-sized arteries of unknown cause. Recently reported that, in skin, small to medium-sized arteries of the dermis-subcutis boundary are affected in a stage-specific sequence.[3]

It usually occurs in young women range aged 20-42 years. However, although rare, it may also occur in children younger than 10 years and over 65 years. Its overall incidence is 4/1,000,000 in population.[1] Systemic hypertension, acrocyanosis, Raynaud's phenomenon, primer headache, venous thrombosis, valvulopathy, spontaneous abortions, seizures, renal involvement, and vascular dementia are other manifestations seen in SS.[4] Antiphospholipid antibodies may be found in approximately half of the patients with SS; some authors suggest that such patients be classified as primary antiphospholipid syndrome.[5] There is no effective drug treatment for this disease, which has a slow and progressive clinical course.[6]

In this article, we aimed to present a 33-year-old woman with cerebrovascular ischemic disease, livedo

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racemosa, history of three miscarriages, mitral valve insufficiency, protein S deficiency and sinus vein thrombosis who was diagnosed with SS, a disease rarely encountered in the literature.

CASE REPORT

A 33-year-old woman admitted to our neurology polyclinic with the complaints of headache, nausea, vomiting, blurred vision lasting for years. From her history, it was learned that headache was unilateral (sometimes in the right half of the face and sometimes in the left side), pulsating in nature without aura, accompanied with nausea and vomiting, lasting more than 4 hours and did not respond to paracetamol. She had history of cerebrovascular infarct occurred when she was 9 and 27 years old and three miscarriages. She has been having persistent cutaneous lesions on the upper and lower extremities and trunk for the last 15 years. There was no significant feature in the family history. Physical examination was normal. Neurological examination did not reveal any pathology, except the right hemihypoesthesia. The dermatological examination showed erythematous violaceous lesions with a reticular pattern, localized in the arms, trunk, thighs, and knees [Figures 1a and 1b]. Skin biopsy was performed. The diagnosis of livedo reticularis was made clinically and histopathologically.

Magnetic resonance imaging (MRI) scan of the brain showed encephalomalacic areas in both parietooccipital lobes, predominantly in the right lobe [Figure 2]. Cerebral venous MR angiography was consistent with the left transverse sinus partial thrombosis. Transthoracic echocardiographic examination demonstrated mild fibrotic thickness of mitral valve and mitral insufficiency. The color doppler ultrasonography of arterial system of bilateral lower extremities was normal.

Blood tests including complete blood count, biochemistry (AST 15 U/L normal range 0-31, ALT 14 U/L normal range 0-31, GGT 9.3 U/L 5-36, others biochemistry levels were normal), C3 (1.08 g/l, normal range 0.9-1.8 g/l), C4 (0.162 g/l, normal range 0.1-0.4 g/l), erythrocyte sedimentation rate (14 mm/h, normal range 0-20 mm/h), rheumatoid factor (9.19 ıu/ML, normal range 0-15 ıu/ML), C-reactive protein (3.36 mg/l, normal range 0-5 mg/l), protein C activity (74%, normal range 70-130%), and urinary sediment were normal. Antinuclear antibodies, anti-dsDNA, anticardiolipin IgM, IgG, lupus anticoagulant, antineutrophil cytoplasmic antibodies, anti-smooth muscle, anticentromere, anti-gliadin, anti-ribonucleoprotein, and serology for syphilis, hepatitis B and C viruses, were all negative. Among coagulation tests, protein S activity was low (28%, normal range is 60%-140%), prothrombin time was 25.5 seconds (normal range, 12-14 seconds) and international normalized ratio (INR) was 2.82 (normal range, 2.5-3.5). The patient who was diagnosed with SS and protein S deficiency depending on these findings was given warfarin, monthly procaine penicillin. Because, the patient was followed up as acute rheumatic fever by cardiologist for ten years.

DISCUSSION

SS was first described by Champion and Rook in 1960.[7] It has been called SS since the series of patients reported by Sneddon, an English dermatologist, in 1965.[8] In 1907 Ehrmann distinguished two different patterns

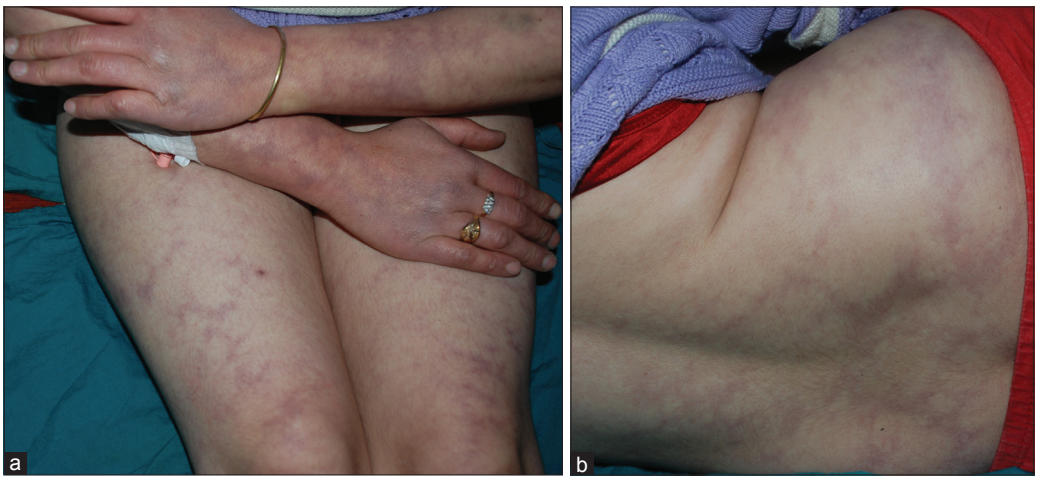

Figure 1: (a, b) The appearance of livedo racemosa

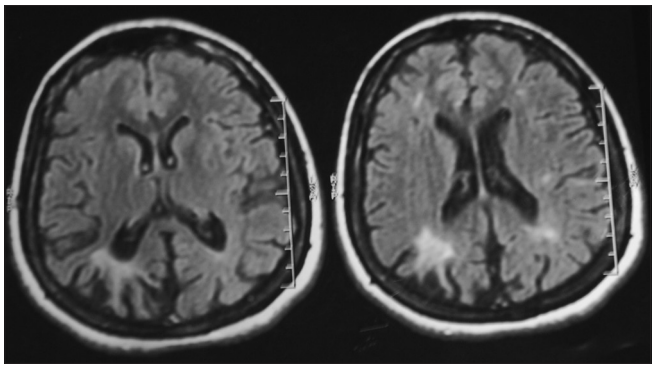

Figure 2: Magnetic resonance imaging showing encephalomalacic areas in parietooccipital lobe

of livedo: The pathological livedo racemosa and the physiological livedo reticularis.[2] SS is accepted that the disease has three forms: Idiopathic form, which is not accompanied with antiphospholipid antibodies or systemic lupus erythematosus (SLE); primary antiphospholipid antibody syndrome-related form; and SLE-associated form with or without the presence of antiphospholipid antibodies. Familial cases were also reported, however, any gene location indicating genetic inheritance has not been identified.[5] In our patient's family, there was no other case showing similar clinical features; antinuclear antibodies, anti-dsDNA, anticardiolipin and antineutrophil cytoplasmic antibodies, lupus anticoagulant were negative.

SS occurs particularly in young adult women and has a progressive chronic course. The mortality rate of 9.5% was reported in a mean observation period of 6.2 years.[6] The complaints of our patient have been lasting since childhood period.

The pathophysiological background of SS is still unknown. The pathogenesis seems to involve a focal thrombotic or embolic process in the arterial or arteriolar vascular system in the skin and the central nervous system. Though some familial cases have been described and genetic predisposition in an autosomal dominant or recessive pattern has been proposed, so far no gene chromosome localization has been found. Because of the increased risk of a thrombotic or embolic process, smoking and oral contraception have been described as risk factors for developing SS.[9]

Livedo racemosa involves persisting irreversible skin lesions red or blue in color with irregular margins, which is localized on the trunk, arms and legs. It appears due to decreased blood flow because of arterial occlusion and local vasoconstriction of skin venules.[1] In our patient, there was diffuse livedo racemosa on the trunk, face, arms and legs.

The symptoms of central nervous system involvement are headache (85%), transient ischemic attack, hemiplegia, hemi-hypoesthesia, hemianopia, dysarthria, central facial paralysis, epileptic seizures, chorea, tremor, myelopathy, and encephalopathy.[9] Headache is a symptom commonly encountered and is accepted as an indicator of increased risk of stroke.[10,11] Epileptic episodes were reported to occur more frequently among antiphospholipid antibody positive patients.[12] Antiphospholipid antibodies were negative in our patient and epileptic seizures were not observed.

Ischemic or valvular type cardiac involvement may occur. Valvular involvement usually appears on the mitral valve.[13] Mild or moderate arterial hypertension is found in 60-80% of the patients.[9] Our patient did not have hypertension, but transthoracic echocardiographic examination demonstrated slight fibrotic thickness of mitral valve and mitral valve insufficiency.

Other system involvements that may be seen in SS are ocular involvement (50-70%), gastrointestinal, renal involvements (50-70%), and venous occlusions.[9]

There is not any effective treatment available for this disease; corticosteroids, anti-platelets, and beta-adrenergic blockers have been studied, but, these agents have not been found to be effective in the majority of the patients.[9] However, anticoagulants and the agents inhibiting platelet aggregation are accepted as the most efficacious modalities.[14] The patients should avoid smoking, obesity and the use of oral contraceptives including estrogen.[9] Our patient who also had protein S deficiency was given oral anticoagulant and she was asked to come for follow-up.

In conclusion, a multidisciplinary approach is necessary for SS that occurs in young women and leads to significant morbidity with recurrent strokes, abortions, ischemic cardiac disorder. Since it has a progressive course, clinical follow-up visits, and regular MRI and transthoracic echocardiographic examination controls should be scheduled. There is no effective drug treatment available; the patients should avoid smoking and the use of contraceptive drugs including estrogen because of the risks of arterial wall lesions and thrombosis.

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